Listing from parent application Serial No. 08/738,544, filed on October 24, 1996 (now US Patent No. 5,783,431) is also submitted.

Claims 27-50 are pending in this application.

The Rejection Under 35 U.S.C. § 112 Is Improper

Claims 34, 35, 41, 42, 45, 47, 49, and 50 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleges that the specification does not provide written support for genetic libraries that express the biosynthetic genes for: polyketides, peptides, glycosides, aminoglycosides, mevalonic acid, and glucose transfer systems (as recited in claims 34 and 45), and beta lactams, macrolides, alkaloids, bryostatins, carotenoids, steroids, and retinoids (as recited in claims 35 and 47). Applicants respectfully disagree.

According to the case law, in order to provide an adequate written description, the specification must reasonably convey to the artisan that the inventor had possession at that time of the claimed subject matter. While a patent applicant does not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991) (citing *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989)).

The Examiner acknowledges that the Applicants have pointed to disclosure of the various antibiotics and multiple protein systems mentioned in the claims in the previous Amendment filed February 10, 2000. The Examiner, however, alleges that "this is not

disclosure of genetic libraries that express the claimed protein systems and multiple protein systems that synthesize the claimed species of molecules." Applicants respectfully disagree.

First, Applicants respectfully point out that these compounds are listed as examples of compounds produced by the myriad of donor organisms that can be used to prepare combinatorial gene expression libraries of the invention. The specification teaches that donor organisms can be used to provide genetic material for the creation of the claimed combinatorial gene expression libraries (page 23, lines 22-24; page 31, lines 3-5). For example, in Section 5.1.1, entitled "Donor Organisms", the specification teaches that donor organisms such as marine microbes produce marinone which is a product of polyketide and mevalonic acid biosynthetic pathways (page 25, lines 21-23). In the same section, the specification provided Table II at page 29, which lists desirable donor organisms for making gene libraries and the chemical nature of exemplary compounds of interest, e.g., "alkaloids and glycosides" (under the group "Higher Plants"); alkaloids (under 'Insects"); "bryostatins" (under "Bryozoans"); "carotenoids, retinoids, and steroids" (under "Birds" and "Mammals"). Applicants respectfully submit that not only are the species of molecules mentioned, they are disclosed in a context that leads directly to combinatorial gene expression libraries that express the claimed protein systems that synthesize them. A skilled artisan, after reading the instant specification, would have understood it to be desirous to make combinatorial libraries containing the above-mentioned biosynthetic systems.

In section 5.1.3, the specification teaches that the host organism for making the combinatorial gene expression libraries may comprise an efflux system. "When the libraries are used for the purpose of generating secondary metabolites, the toxicity of the compounds can lead to under-representation of these productive host organisms in the library." (page 47, lines 19-23). On page 48, lines 9-12, the specification states that efflux

systems can pump out a variety of molecules including "polyketide antibiotics." The efflux systems listed in Table III (on page 49; efflux system for "beta-lactams") are meant to counteract this toxicity by secreting the compound so to avoid its accumulation inside the library cell. Therefore, Applicants submit that, based on the teachings in the specification, one of ordinary skill in the art would have understood that such libraries that make the toxic polyketide or beta-lactam compounds to be pumped out by the efflux system are contemplated. The libraries that make the toxic compounds are expected to contain the relevant biosynthetic genes, and thus, the support is provided inherently in the disclosure of the biosynthesis of such toxic products by the library cells.

In section 5.1.6, the specification teaches the construction of biased combinatorial gene expression libraries that uses probes for pre-selecting fragments of DNA isolated from the donor organisms. On page 62, lines 27-32, it is stated that "The preselected fragments of DNA contain genes encoding partial or complete biosynthetic pathways, and may be preselected by hybridizing to an initial or archival DNA library a plurality of probes prepared from known genes that may be related to or are involved in producing compounds of interest." It is further stated that cloned biosynthetic pathways, such as polyketide (page 63, lines 35-36), peptide synthases and aminoglycoside synthases (page 66, lines 14-15) can provide probes for pre-screening. Thus, Applicants submit that it would have been clear to one of ordinary skill in the art that the pre-selected DNA that are used to make the claimed libraries, would contain genes that are related to or are involved in producing polyketides, peptides and aminoglycosides. Here, Applicants' disclosure not only teaches what genes are desired and expected to be in the claimed biased combinatorial gene expression libraries, the method for making such claimed libraries are also specifically described.

"[I]psis verbis disclosure is not necessary to satisfy the written description requirement of section 112." Fujikawa v. Wattanasin, 93 F.3d 1559, 39 U.S.P.Q. 2d 1895, 1904 (Fed. Cir. 1996). The test for sufficiency of support is whether the disclosure relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985), citing to *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983); *Wang Labs., Inc. v Toshiba Corp.*, 993 F.2d 858, 865 (Fed. Cir. 1993) citing to *Vas-Cath Inc. v Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)); and must enable such a person to make and use the claimed subject matter, without first having to perform unduly extensive experimentation. *Hybritech Inc. v Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

In view of the foregoing, Applicants submit that, although ipsis verbis disclosure is not present, the various teachings of the specification reasonably convey to persons skilled in the art that the inventor had possession of the claimed gene expression libraries in question, and that one of ordinary skill in the art would recognize that Applicants invented the claimed gene expression libraries. Accordingly, the Examiner's rejection is in error.

In response to the Examiner's allegation that documentation was not provided to support the assertion that the biosynthetic genes for the species of molecules recited in the claims are well known, Applicants submit that such information would indeed have been easily attainable to one of skill in the art. A simple literature search[1] revealed the following exemplary articles that disclose information relevant to the invention: mevalonic acid (Re et al., 1995, *Plant J* 7:771), macrolides (Donadio et al., 1991, *Science* 252:675), carotenoids

[1] Three preliminary terms (the name of the protein of interest/ pathway/ sequence) were used to search PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and required no laborious refining to identify the pertinent articles.

(Misawa et al., 1995, *J Bacteriol* 177:6575), steroids (Her et al., 1995, *Genomics* 29:16), oxytetracycline (Khosla et al., 1993, *J Bacteriol* 175:2197), puromycin (Lacalle et al., 1992, *EMBO J* 11:785), doxorubicin (Grimm e al., 1994, *Gene* 151:1), mithramycin (Lombo et al., 1996, *Gene* 172:87), polyketide biosynthesis (Blanco et al., 1993, *Gene* 130:107)[2]. Accordingly, Applicants submit that information on probes and genes that are related to or involved in the biosynthetic pathways of the recited species of molecules are commonly accessible. A patent application need not include in the specification that which is already known to and available to the public. *Paperless Accounting Inc. v. Bay Area Rapid Transit System*, 804 F.2d 659, 231 U.S.P.Q. 649 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 933 (1987).

In view of the foregoing, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Rejection Under 35 U.S.C. § 102 Is Obviated

Claims 27-34, 36-41, 43-46, and 48-50 are rejected under 35 U.S.C. § 102(f) because allegedly, Applicants did not invent the claimed subject matter.

The Examiner alleges that U.S. Patent No. 5,824,485 (the '485 patent) discloses a gene expression library comprising cDNA or genomic DNA fragments isolated from a plurality of species of different organisms; and provides guidance to isolate donor organisms from an environmental sample (e.g., soil, deposits near hot springs or thermal vents, freshwater or seawater filtrates, or marine or estuarine sediments), to make selected libraries that encode proteins that are involved in secondary metabolism, and to use vectors for introduction of the library into host cells. As such, the Examiner alleges that the '485

[2] Please note that in order to not unduly burden the Examiner, only abstracts are submitted herewith as Exhibit A. However, if the Examiner would prefer, complete references can be provided upon request.

patent anticipates the claimed invention of this application because the inventive entities for both are different.

The present application is a divisional application of application 08/783,944 (now U.S. Patent No. 5,783,431), which is a continuation-in-part of application no. 08/639,255 (now U.S. Patent No. 5,824,485). The inventive entity of U.S. Patent No. 5,824,485 was Katie A. Thompson, Lyndon M. Foster, Todd C. Peterson, Nicole M. Nasby, and Paul Brian. With the addition of Katie A. Thompson as a co-inventor by the Petition to Amend Inventorship filed on February 10, 2000, the inventive entity of this application is now correct.

Applicants submit that Nicole M. Nasby is not a co-inventor of the presently claimed subject matter which pertains to combinatorial gene expression libraries. Evidence of this comes from the Verified Statement of Facts in Support of Correction of Inventorship Pursuant to 37 C.F.R. § 1.48(a) during the prosecution of the '485 patent (submitted herewith as Exhibit B along with all of the documents filed on August 7, 1997). Paragraph 4 of the aforementioned document shows that Nicole M. Nasby was responsible for only the conception and reduction to practice of methods to make the host organisms more amenable to manipulations in the laboratory and high throughput screening by encapsulating the library-containing host organisms in a semi-solid matrix. Although libraries using this type of matrix are claimed in the '485 patent (see Claim 18), they are not claimed in the present application. Due to the complete absence of her contribution from the claims of the present application, Nicole M. Nasby is not a co-inventor of the present application.

Applicants submit that all of the inventors of the claimed subject matter are properly identified and therefore, the rejection under 35 U.S.C. § 102(f) should be withdrawn.

CONCLUSION

Applicants respectfully request that the remarks of the present response be entered and made of record in the instant application. Withdrawal of the Examiner's rejections and allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: September 18, 2000

By: [signature] 40,258

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Enclosures